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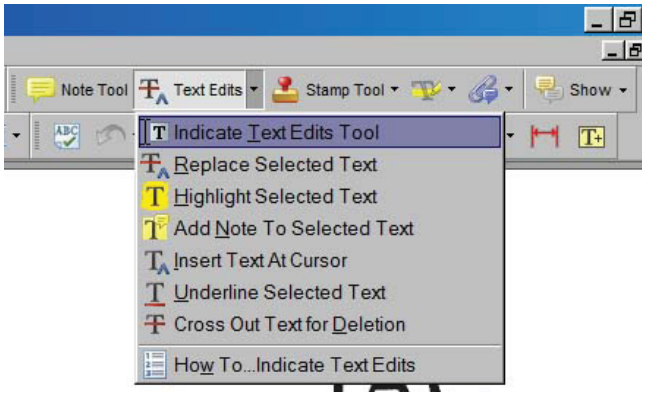

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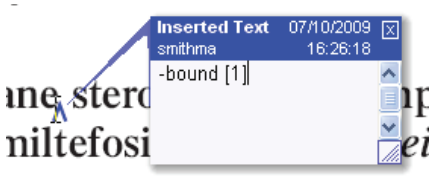

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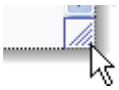

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Prodromal angina is associated with myocardial salvage in acute ST-segment elevation myocardial infarction

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Aims Previous studies have shown that prodromal angina (PA) occurs frequently in acute myocardial infarction (MI) patients. However, the potential benefits of PA on ischaemic myocardial damage remain unknown.

Methods and results One-hundred and fifty-four patients with acute ST-segment elevation MI successfully treated with primary percutaneous coronary intervention (PPCI) were prospectively evaluated for new-onset PA in the week preceding infarction and other factors known to influence myocardial salvage. Cardiovascular magnetic resonance was performed 8 ± 3 days after MI for the assessment of area-at-risk (AAR), MI size, myocardial haemorrhage (MH), microvascular obstruction (MO), and myocardial salvage index (MSI).

Patients with PA ($n = 60$) compared with those without PA ($n = 94$) showed similar AAR but significantly smaller MI size leading to larger MSI (0.53 ± 0.27 vs. 0.32 ± 0.26, $P < 0.001$). Additionally, patients with PA had lower incidence of MH (18 vs. 33%) and MO (22 vs. 46%) than non-PA patients (both $P < 0.05$). At univariate analysis, higher MSI was associated with new-onset PA, lower myocardial oxygen consumption before PPCI, shorter time-to-PPCI, and higher post-procedural TIMI flow-grade. Neither collateral circulation nor medications administered before PPCI were associated to MSI. After correction for other covariates by multivariate analysis, new-onset PA remained significantly associated with MSI (β-value: 0.352, $P < 0.001$).

Conclusion In acute MI patients, new-onset PA is associated with higher MSI independent of others factors known to influence jeopardized myocardium, as well as with less microvascular damage.

Keywords Prodromal angina • Myocardial infarction • Cardioprotection

Introduction

The pathophysiological basis of ischaemic myocardial damage has been deeply investigated thoroughly in animal models of reperfused and non-reperfused myocardial infarction (MI), yet remains poorly understood in humans.[1,2] This apparent paradox may be explained considering that: (i) in the clinical scenario many variables, which are difficult to account for, may influence ischaemic myocardial damage; (ii) the complexities inherent in the study of jeopardized myocardium in humans. Experimentally, most of the variation in infarct size is related to area-at-risk (AAR) and reperfusion status, and to a lesser extent to collaterals, haemodynamic determinants of myocardial metabolic demand, and medications.[1] Moreover, brief episodes of myocardial ischaemia before sustained ischaemia reduces MI size, a phenomenon known as ischaemic preconditioning (IPC).[3] In humans, acute MI is often preceded by prodromal angina (PA), and previous clinical studies suggested that PA may limit MI size through various mechanisms, including collaterals

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recruitment,[4] reperfusion facilitation,[5] and IPC.[6–11] However, these studies were conducted in highly selected populations and limited by the retrospective nature. Therefore, whether PA confers cardioprotection in patients with acute MI is still a matter of debate.

Cardiovascular magnetic resonance (CMR) is a valuable tool to investigate this issue because it allows an accurate and comprehensive assessment of ischaemic myocardial damage in the early post-infarction period.[12,13] Based on these premises, we prospectively studied a cohort of acute MI patients with the aim of examining the influence of PA on myocardial salvage using CMR.

Methods

Study population

Between January 2011 and January 2012, 212 consecutive acute ST-segment elevation MI patients [95 at Fondazione 'G. Monasterio'-Italy, Pisa & Massa (Centre A), 63 at La Sapienza University, Rome, Italy (Centre B) and 54 at Centro Cardiologico Monzino, Milan, Italy (Centre C)] were prospectively evaluated for study enrolment. CMR was performed 8 ± 3 days after MI. Inclusion criteria were: (i) chest pain suggestive of myocardial ischaemia lasting >30 min; (ii) ECG showing ST-segment elevation >0.1 mV in ≥2 limb leads or >0.2 mV in ≥2 contiguous precordial leads, or presumed new left bundle-branch block; (iii) successful treatment with primary percutaneous coronary intervention (PPCI) within 12 h from symptoms onset; (iv) ability to provide detailed clinical history. Exclusion criteria were prior MI or revascularization, atrial fibrillation, Killip class >II, renal failure [creatinine >2 mg/dL (0.226 μmol/dL)] and contraindications to CMR. The study complied with the Declaration of Helsinki, the Ethics Committee approved the research protocol, and informed consent was obtained from each subject.

Clinical variables

Within 5 days from admission, clinical history was recorded from each patient by one of the physicians participating to the study. Particular attention was paid to assess new-onset PA, defined as one or more episode of typical chest pain lasting ≤30 min at rest or on effort within 7 days from the infarction.[5,6] The number of PA episodes and the time intervals between the first and last episode of PA and infarction were registered. Time-to-PPCI was defined as the interval time between the onset of continuous chest pain and the re-opening of the infarct-related artery by PPCI.

Blood pressure and heart rate values before PPCI were collected from clinical documents completed in the ambulance, emergency department, intensive coronary care unit, and catheterization laboratory. Mean rate pressure product (mRPP), which correlates with myocardial oxygen consumption before PPCI,[14] was calculated by multiplying mean systolic blood pressure and mean heart rate. The use of nitrates, morphine, beta-blockers, and Gp IIb/IIIa before PPCI were also recorded.

Coronary angiography analysis

All coronary angiograms were analysed at Centre A by an experienced physician blinded to clinical and CMR data. The TIMI flow-grade of the infarcted-related artery was assessed before and after PPCI. The grade of epicardial collaterals to the infarcted-related artery was evaluated according to Rentrop *et al.*[15]; collateral circulation was defined as Rentrop grade ≥2. Double- and triple-vessel coronary disease were diagnosed when a ≥75% stenosis in one or two vessels remote from the infarct-related artery, respectively. All patients received dual anti-platelet therapy upon admission.

CMR protocol

CMR studies were performed at Centre A with 1.5-T unit (CVi, GE-Healthcare, Milwaukee, USA), at Centre B with 1.5-T unit (Avanto Siemens, Erlangen, Germany), and at Centre C with 1.5-T unit (Discovery MR450, GE-Healthcare, Milwaukee, USA). All studies were performed using dedicated cardiac software, phased-array surface receiver coil, and electrocardiogram triggering. A similar CMR study protocol was followed in all centres (see Supplementary material online). Breath-hold steady-state free-precession cine CMR was performed in vertical and horizontal long-axis, and in short-axis orientations. In short-axis, both ventricles were completely encompassed by a stack of contiguous slices. Breath-hold black-blood T2-weighted short inversion-time inversion-recovery fast spin-echo (T2w-imaging) was performed in short-axis orientation for AAR quantification. Breath-hold contrast-enhanced segmented T1-weighted inversion-recovery gradient-echo sequence [late-gadolinium enhancement (LGE)-imaging] was used to quantify MI and microvascular obstruction (MO). 10–20 min after an intravenous bolus of 0.1 mmol/kg Gadolinium-BOPTA (Multihance-Bracco, Milan, Italy) or 0.2 mmol/kg Gadolinium-BOPTA Gadolinium-DOTA (Dotarem Guerbet Roissy, France) LGE-imaging was performed. Inversion time was individually adapted to nullify the signal of remote myocardium (usual range 220–300 ms).

Image analysis

All CMR studies were analysed off-line by the consensus of two experienced observers at Centre A using a workstation (Advantage Workstation, GE-Healthcare, Milwaukee, USA) with a dedicated software (MASS 6.1, Medis, Leiden, the Netherlands). Operators were unaware of clinical and angiographic data. Analysis was started by scoring T2w-imaging quality using a 4-grade score: (1) poor, (2) moderate, (3) good, and (4) excellent. Only exams with a score >2 were included. T2w-imaging was used to quantify AAR and visualize myocardial haemorrhage (MH). Myocardium with a signal intensity (SI) >2 SD above mean SI of remote non-infarcted myocardium was considered AAR. Attention was paid to exclude increased SI from the blood adjacent to endocardium ('slow flow'). MH was defined as a hypo-intense area in the core of AAR. When present, MH was included in hyper-intense myocardium for AAR calculation.[12] On post-contrast imaging, LGE was considered present if SI of the hyperenhanced myocardium was >5 SD above the mean SI of remote myocardium,[16] whereas MO was defined as hypo-enhanced region within the infarcted myocardium. When present, MO was included in the hyper-intense myocardium for LGE quantification. Left-ventricular (LV) LGE and MO were expressed as absolute (grams) or relative (LV percentage) value. Infarct transmurality was calculated as the ratio of mean thickness of hyperenhanced myocardium to mean thickness of the corresponding myocardial wall, multiplied by 100. Cine CMR was used to derive LV volumes, ejection-fraction, regional wall motion, and mass. For LV wall motion analysis, we used the 17-segment model proposed by AHA[17] (segment 17 was excluded from analysis). Regional wall motion was scored for each segment from 1 to 5 (1: normal/mild hypokinesia; 2: moderate hypokinesia; 3: severe hypokinesia; 4: akinesia; 5: dyskinesia). Wall motion score index (WMSI) was determined as the sum of segmental scores divided by the number of segments.[13]

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Statistical analysis

Continuous variables were expressed as mean ± SD or median (25th–75th percentiles). Kolmogorov–Smirnov test was used to assess the normality of data distribution, and variables distributed non-normally were logarithmically transformed. Categorical variables were expressed as frequency with percentage. Student's independent *t*- or Mann–Whitney tests were used, as appropriate, to compare continuous variable differences. Comparisons between categorical variables were made with χ^2 test or Fisher's exact test, if an expected cell count was <5. Correlations between continuous variables were assessed using Pearson's (*r*) coefficient or Spearman's rho, as appropriate. Univariate linear regression analysis was utilized to determine the association of variables with MSI. Variables known to influence MSI were tested as potential covariates.[1–10] Multivariate linear regression analysis was used to evaluate the influence of covariates on MSI. Variables with a *P*-value <0.10 at univariate analysis were entered in the multivariable model as covariates. Statistical analysis was performed by SPSS software for Windows (15.0 release; SPSS, Chicago, IL, USA); all tests were two-tailed at 5% significance level.

Results

Study population

Thirty-five (18%) patients were excluded from the study because of inadequate T2w-imaging quality, thus leaving a total of 154 patients for the analysis (124 men, age 62 ± 11 years; *Figure 1*). Patients were dichotomized according to the presence ($n = 60$) or absence ($n = 94$) of new-onset PA. Baseline characteristics are summarized in *Table 1*. Peak troponin I was lower in patients with than those without PA. Notably, mRPP before PPCI, TIMI flow-grade before and after PPCI and Rentrop-grade were similar in the two groups. Nitrate use before PPCI was more common in patients with PA.

Prodromal angina characteristics

The characteristics of PA are summarized in *Table 2*. Twenty-eight patients (47%) referred only one episode of PA, whereas the remaining 32 patients (53%) had repeated episodes in the week preceding infarction. Notably, 58 (97%) and 31 (52%) patients experienced the last episode of PA within 48 and 6 h from infarction, respectively. The two patients presenting PA > 48 h had one single episode of angina occurring 55 and 72 h before infarction.

Prodromal angina and ischaemic myocardial damage

CMR findings are summarized in *Table 3*. Patients with and without PA showed similar AAR although LGE extent was significantly lower in patients with PA, resulting in higher MSI. Infarct transmurality was also lower in patients with PA compared with those without PA (*Figure 2*). As a result, patients with PA had better regional and global LV systolic function than patients without PA. In addition, aborted MI (evidence of AAR on T2w-imaging but the absence of LGE on LGE-imaging) was more commonly observed in patients with than those without PA [8(13%) vs. 3(3%), $P = 0.017$]. Patients with PA also showed lower incidence of MH

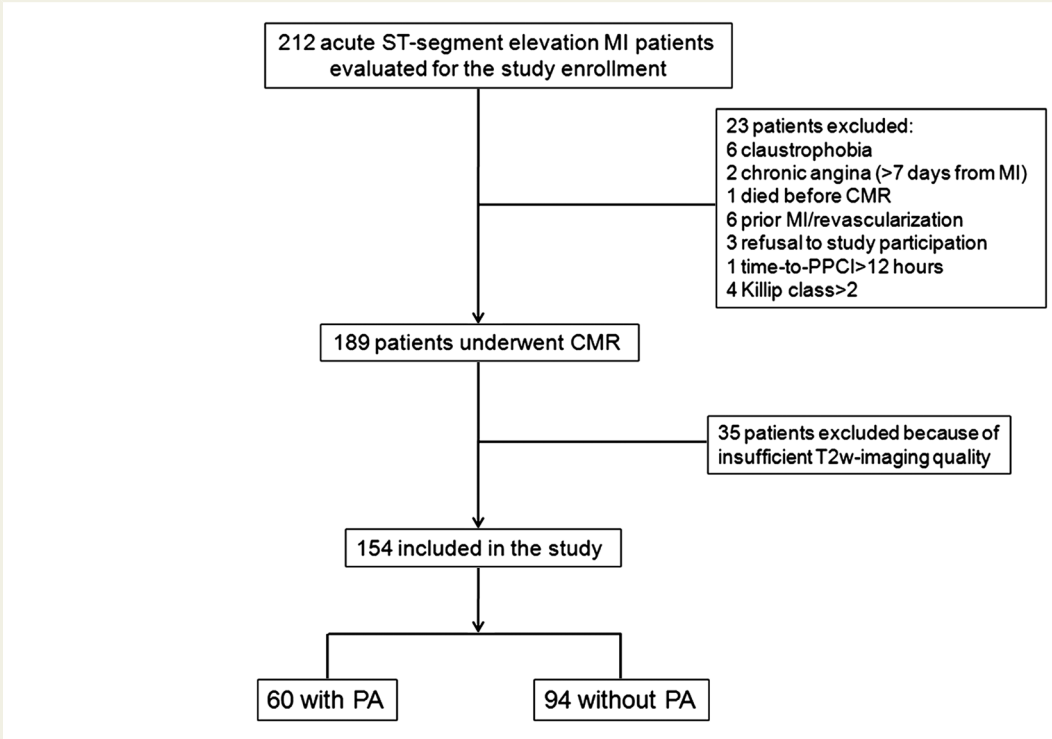

Figure 1 Study protocol.

Table 1 Baseline patients characteristics

Characteristics	Presence of PA ($n = 60$)	Absence of PA ($n = 94$)	*P*-value
Age (years)	60 ± 12	63 ± 10	0.146
Male, *n* (%)	49 (82)	75 (80)	0.774
Cardiovascular risk factors, *n* (%)			
Hypertension	30 (50)	54 (58)	0.328
Diabetes	9 (15)	17 (18)	0.598
Hypercholesteraemia	23 (38)	42 (45)	0.404
Family history CAD	22 (37)	39 (42)	0.516
Current smokers	32 (53)	43 (46)	0.391
Killip class II	2 (3)	7 (7)	0.299
Peak troponin I (ng/dL)	31 [10–77]	71 [22–115]	0.002
Time-to-PPCI (min)	245 ± 162	248 ± 166	0.908
Haemodynamic parameters before PPCI			
Mean systolic BP (mmHg)	138 ± 19	135 ± 17	0.232
Mean diastolic BP (mmHg)	82 ± 11	78 ± 10	0.004
Mean heart rate (bpm)	76 ± 13	75 ± 16	0.692
Mean RPP ([bpm] mmHg)	10 430 ± 2419	10 136 ± 2846	0.514
Medications before PPCI, *n* (%)			
Beta-blocker	7 (12)	9 (10)	0.659
Nitrate	29 (51)	30 (33)	0.030
Morphine	13 (22)	22 (24)	0.833
Gp IIb/IIIa	7 (11)	18 (19)	0.152
Catheterization laboratory data			
Infarct-related artery, *n* (%)			0.497
LAD	33 (55)	44 (46)	
LCx	8 (13)	12 (13)	
RCA	19 (32)	38 (41)	
Double-vessel disease, *n* (%)	20 (33)	28 (30)	0.643
Triple-vessel disease, *n* (%)	7 (12)	7 (7)	0.324
Use of Gp IIb/IIIa, *n* (%)	26 (44)	42 (45)	0.968
Thrombus aspiration *n* (%)	30 (50)	51 (54)	0.606
TIMI flow-grade pre-PPCI, *n* (%)			0.647
0/1	55 (92)	88 (94)	
2/3	5 (8)	6 (5)	
TIMI flow-grade post-PPCI, *n* (%)			0.320
0/1	2 (3)	1 (1)	
2/3	58 (97)	93 (99)	
Presence of collaterals, *n* (%)	5 (8)	12 (13)	0.392
Rentrop grade	0.23 ± 0.70	0.32 ± 0.78	0.489
Medications at discharge, *n* (%)			
ACE-i/ARBs	48 (84)	80 (87)	0.640
Beta-blocker	49 (86)	74 (80)	0.387
Statins	54 (95)	89 (97)	0.646
Spironolactone	10 (17)	21 (22)	0.440

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; LAD, left-anterior descending coronary artery; LCx, left circumflex coronary artery; PA, prodromal angina; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; RPP, rate pressure product; TIMI, thrombolysis in myocardial infarction.

and MO. When including only patients with pre-PPCI TIMI flow-grade ≤1 and Rentrop-grade ≤1 ($n = 128$), MSI remained higher and infarct transmurality was lower in patients with PA than those without PA (0.49 ± 0.26 vs. 0.34 ± 0.26, $P = 0.003$ and 57 ± 32 vs. 72 ± 30%, $P = 0.029$; respectively).

The influence of PA on jeopardized myocardium

In the overall population, MSI was 0.40 ± 0.28 and had a normal distribution (Kolmogorov–Smirnov: 1.041, $P = 0.229$). There was

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Table 2 Characteristics of prodromal angina

Characteristics	Range	Median [25th–75th]
Number of episodes of PA	1–9	2 [1–3]
Duration of first PA episode (min)	2–30	15 [6–20]
Time from PA first to acute MI (h)	0.2–167	10 [4–34]
Duration of last PA last (min)	3–30	20 [10–25]
Time from PA last to acute MI (h)	0.2–72	6 [1–22]

PA, prodromal angina; MI, myocardial infarction.

Table 3 Cardiovascular magnetic resonance characteristics

Variables	Presence of PA ($n = 60$)	Absence of PA ($n = 94$)	*P*-value
Area-at-risk (g)	29 ± 17	30 ± 18	0.832
LGE extent (g)	10 [3–24]	18 [9–30]	0.009
LGE extent (% LV)	8 [3–19]	14 [8–23]	0.007
MSI	0.53 ± 0.27	0.32 ± 0.26	<0.001
MI transmurality (%)	53 ± 33	74 ± 29	0.001
MH, *n* (%)	11 (18)	31 (33)	0.047
MO, *n* (%)	13 (22)	40 (43)	0.008
MO extent (g)	5 [4–7]	4 [2–8]	0.437
LV-EDV (mL)	141 ± 36	145 ± 36	0.515
LV-ESV (mL)	64 ± 29	71 ± 26	0.136
LV-SV (mL)	77 ± 19	74 ± 21	0.463
CI (mL/m^2)	2.69 ± 0.69	2.71 ± 0.74	0.848
LV-EF (%)	56 ± 10	52 ± 10	0.029
LV-mass (g)	135 ± 30	132 ± 37	0.529
LV-WMSI	1.502 ± 0.334	1.660 ± 0.405	0.030

CI, cardiac index; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular; MI, myocardial infarction; MO, microvascular obstruction; MSI, myocardial salvage index; WMSI, wall motion score index.

a weak inverse relationship between MSI and time-to-PPCI ($r = -0.173$, $P = 0.031$). Dichotomizing patients on the basis of PA, MSI remained inversely related to time-to-PPCI in patients without PA ($r = -0.291$, $P = 0.004$) but not in those with PA ($r = -0.025$, $P = 0.850$). Similarly, in the overall population, MSI was inversely related to pre-PCCI mRPP ($r = -0.191$, $P = 0.019$), but when patients were dichotomized on the basis of PA, MSI remained inversely related to pre-PPCI mRPP in patients without PA ($r = -0.295$, $P = 0.004$) but not in those with PA ($r = -0.103$, $P = 0.422$) (*Figure 3*). Notably, in patients with PA, there was a positive relationship between MSI and the number of PA episodes (Spearman's rho = 0.332, $P = 0.010$). On the other hand, no relationship was observed between MSI and the time elapsed from the first or last episode of PA to infarction ($r = 0.008$, $P = 0.949$ and $r = -0.133$, $P = 0.316$, respectively). At univariate linear regression analysis, shorter time-to-PPCI, lower pre-PPCI mRPP, higher post-PPCI TIMI flow-grade, and the occurrence of PA were significantly associated with larger MSI (*Table 4*). At multivariate linear regression analysis, the occurrence of PA remained significantly associated with MSI after correction for pre- and post-PPCI TIMI flow-grade, pre-PPCI mRPP, and time-to-PPCI (*Table 5*).

Discussion

We showed that patients with acute MI experiencing new-onset PA in the week preceding the infarction had higher MSI, less infarct transmurality, and lower incidence of MH and MO than patients without PA, resulting in better regional and global LV systolic function. Noteworthy, the occurrence of PA remained significantly associated to higher MSI even after correction for other factors implicated in ischaemic injury, including pre- and post-procedural TIMI flow-grade, myocardial oxygen consumption before PPCI, and time to revascularization. Moreover, in patients with PA, the degree of MSI was positively related to the number of episodes of PA.

Our study is novel in so far as we assessed the impact of new-onset PA on myocardial salvage using CMR in the early post-infarction period after accounting for factors known to influence the ischaemic damage and which could be readily assessed. In comparison to patients without PA, those with new-onset PA showed greater MSI, as a result of smaller MI size, less infarct transmurality, and lower incidence of MH and MO. Previous studies have reported that coronary occlusion in the early period of infarction is highly dynamic,[18] and Andreotti *et al.*[5] have shown that in acute MI patients treated with thrombolysis, the occurrence of PA results in more rapid reperfusion, thus leading to smaller infarct size. However, in our study, the residual blood flow to the myocardium at risk through the infarct-related artery or epicardial collaterals was similar in patients with and without PA. Additionally, when the analysis was limited to patients with pre-procedural TIMI flow-grade ≤1 and Rentrop-grade ≤1, the degree of MSI remained higher and infarct transmurality was lower in patients with PA. These data indicate that IPC is likely a mechanism by which new-onset PA protects the myocardium at risk.[3]

Experimentally, the cardioprotective effect of IPC has been confirmed by a plethora of data derived from diverse animal species. In particular, it has been demonstrated that repetitive brief episodes of ischaemia protect the myocardium from the subsequent sustained ischaemia, limiting final MI size.[3,19] Our findings expand previous observations made in humans that indentified IPC as the putative mechanism underlying the beneficial effects of new-onset PA on post-infarction LV function recovery,[4,6,7,9,10] as well as on short- and long-term prognosis.[8,20,21] However, prior studies were limited by the lack of direct measure of salvaged myocardium and by their retrospective nature which did not allow to adjust for factors potentially influencing myocardial salvage. In our study, we prospectively analysed the variables known from previous experimental and clinical studies to intervene on ischaemic damage. Noteworthy, multivariate analysis confirmed that new-onset PA in the week preceding MI was independently associated with a higher MSI. Recently, in a subgroup analysis of a randomized controlled trial demonstrating the cardioprotective effect of exenatide

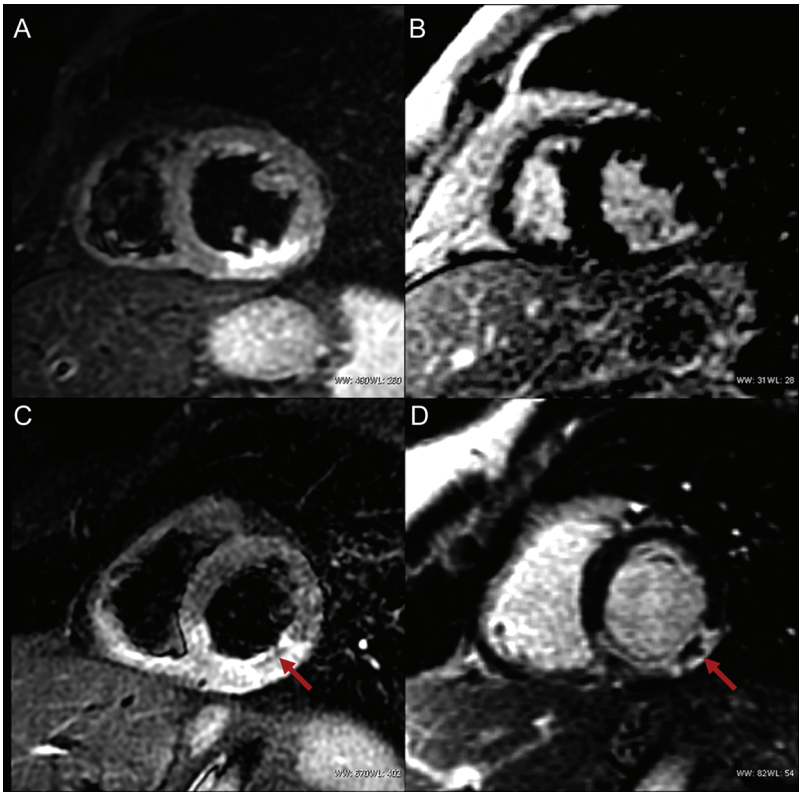

Figure 2 T2w-imaging (*A* and *C*) and LGE-imaging (*B* and *D*) in two patients with acute infero/lateral MI. One patient referred two episodes of PA within 48 h from infarction (upper panel), whereas the second patient was asymptomatic in the week preceding MI (bottom panel). Both patients presented the same angiographic characteristics (pre-/post-PPCI: 0/3; Rentrop-grade: 0) and similar time-to-PPCI (233 vs. 247 min) and mRPP before PPCI (10 143 vs. 10 127 [bpm] mmHg), nevertheless the patient with PA had higher MSI (0.68 vs. 0.05) and lower infarct transmurality (34 vs. 98%) when compared with patient without PA. Additionally, MH (*C*, arrow) and MO (*D*, arrow) were detected only in the patient without PA.

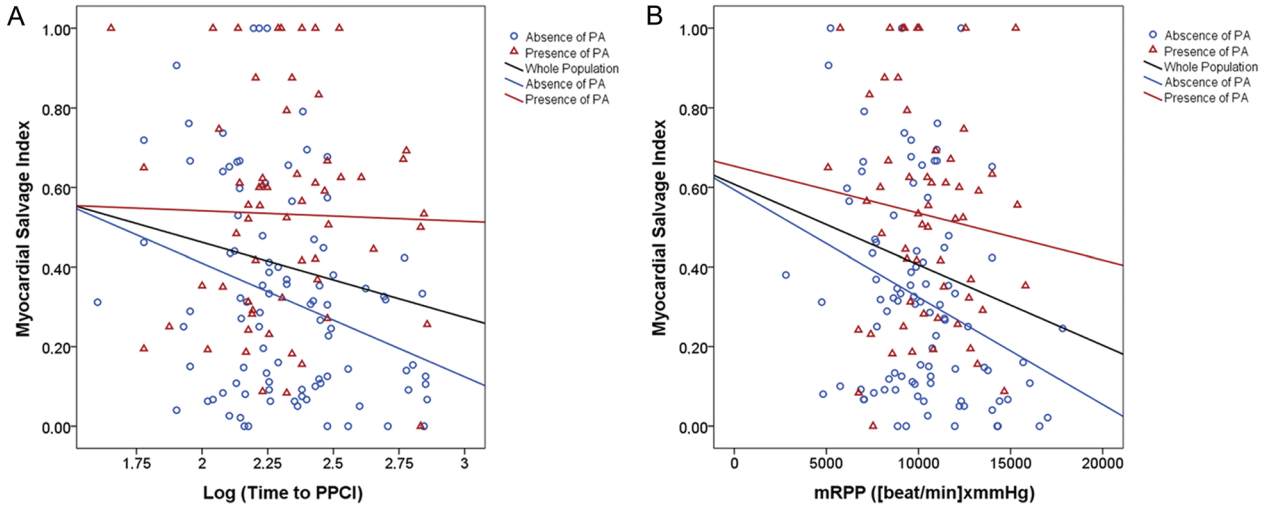

Figure 3 Scatter plots and regression lines of MSI and logarithm (Log) of time-to-PPCI (*A*) and mRPP before PPCI (*B*) in the whole study population (black regression line) and in patients with (red triangles, red regression line) and without PA (blue circle, blue regression line).

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Table 4 Univariate linear regression analysis for MSI determinants

Baseline characteristics	β-value	P-value
Age	0.010	0.901
Female gender	0.072	0.376
Hypertension	0.018	0.825
Diabetes	0.060	0.458
Hypercholesterolaemia	0.024	0.769
Family history of CAD	−0.050	0.543
Current smoking	0.014	0.861
Killip class	−0.029	0.726
Time-to-PPCI	−0.191	0.018
Prodromal angina	0.367	<0.001
Infarct-related artery	−0.012	0.883
TIMI flow-grade pre-PPCI	0.146	0.066
Presence of collaterals	−0.028	0.732
TIMI flow-grade post-PPCI	0.185	0.022
mRPP before PPCI	−0.191	0.019
Beta-blocker before PPCI	0.020	0.808
Nitrate before PPCI	−0.100	0.227
Morphine before PPCI	−0.017	0.841
Gp IIb/IIIA before PPCI	0.083	0.312

Abbreviations as reported in previous tables.

Table 5 Multivariate linear regression analysis for MSI determinants

Baseline characteristics	β-value	P-value
Time-to-PPCI	−0.172	0.018
Prodromal angina	0.352	<0.001
TIMI flow-grade pre-PPCI	0.114	0.121
TIMI flow-grade post-PPCI	0.180	0.013
mRPP before PPCI	−0.217	0.003

Abbreviations as reported in previous tables.

in acute MI patients, Lonborg *et al.*[11] showed that PA in the 3 months preceding MI was associated with higher MSI as quantified by CMR. However, this study had several limitations making the interpretation of the results difficult. First, it cannot be excluded that exenatide influenced the sub-study results; secondly, no data on MH and MO were reported; thirdly, the time interval between PA and infarction was not mentioned.

Experimentally, the cardioprotective effect of IPC is lost if the interval between the preconditioning stimulus and infarction exceeded few hours (classical IPC) to then reappear between 24 and 72 h after the initial IPC stimulus (delayed or 'second window' of IPC).[3,19] In humans, classic IPC has been reported during percutaneous coronary angioplasty[22] and cardiac surgery,[23] and the occurrence of new-onset PA within 24 h from acute MI has been associated with smaller MI size and better post-infarction LV function recovery[9] and prognosis.[20] Other groups have reported that PA within 48 h from acute MI is also associated with enhanced recovery of LV function after infarction[4,8] and better in-hospital prognosis.[7] In our study, all except two patients and more than half of patients experienced the last episode of PA within 48 and 6 h from infarction, respectively, indicating that classical or delayed IPC may account for the cardioprotective effect of PA. However, MSI was not related to the time elapsed from the first or last PA episode to acute MI. The independence of the time interval between episodes of PA and the degree of salvaged myocardium may be explained by the fact that silent ischaemia also contributes to IPC. Although one may argue that silent ischaemia might also occur in patients without PA, it has been reported that patients with PA had higher prevalence of silent pre-infarction ischaemia on 24 h Holter monitoring compared with asymptomatic patients.[24] Furthermore, we also found that in patients with PA, the degree of MSI was positively related to the number of new-onset PA episodes. Whether this finding indicates a cumulative cardioprotective effect of IPC in humans cannot be clarified by our results and merits further investigation. Reasonably, our findings indicate that patients with at least one episode of PA are more likely to be effectively preconditioned than asymptomatic patients, and the likelihood of cardioprotection is positively linked to the increasing number of PA episodes.

Interestingly, we also found that patients with PA had a lower incidence of MH and MO than patients without PA, indicating a more favourable pattern of post-infarction damage. Myocardial haemorrhage invariably denotes a severe damage of coronary microvasculature with leakage of red blood cells from injured vessels, and it occurs only in reperfused MI thereby representing a marker of post-reperfusion damage.[12,25,26] One may speculate that IPC mitigates post-reperfusion damage in humans with a particular beneficial effect on the coronary microvasculature. This finding is consistent with experimental studies showing that IPC minimizes post-reperfusion injury[19] not only acting directly on cardiomyocytes but also by preserving coronary microvasculature function.[27] Notably, in humans Komamura *et al.*[28] demonstrated that in patients with acute anterior MI, the occurrence of new-onset PA is associated with higher post-reperfusion great cardiac vein flow, reflecting better coronary microvascular function and smaller infarct size compared with patients without PA. Similarly, in acute MI patients undergoing PPCI, Takahashi *et al.*[29] reported that no-reflow phenomenon was less commonly observed in patients with PA compared with those without PA.

According to our study results, the assessment of new-onset PA in the week before infarction is of importance in studies testing novel or adjunctive reperfusion strategies aiming to protect the myocardium at risk, since the unbalanced distribution of this variable between the intervention and control groups may alter the final results.

Limitations

This was a three-centre study using different vendor CMR units, even though a similar study protocol was used with centralized data analysis. The determination of AAR by T2-weighted has limitations due to the inherently low signal-to-noise ratio and the susceptibility of signal loss in cardiac structures distant from the

surface coil. However, all CMR units used an SI correction algorithm to homogenize signal, and only patients with CMR exams showing a good or excellent T2-weighted images were included in the study. The parameters of T2-STIR sequence were slightly different across the diverse centres potentially resulting in discrepancies in the quantification of the AAR. We did not provide clinical nor CMR follow-up data. However, the study intended to investigate the pathophysiological factors influencing ischaemic damage in patients with acute MI. It is very likely that the beneficial effects of PA in the early post-infarction period will translate into better LV remodelling at mid- and long-term follow-up. Finally, the assessment of PA relied on the quality of history taking in acutely hospitalized patients.

Conclusion

New-onset PA in the week preceding acute MI is associated with larger myocardial salvage independent of other factors known to influence the jeopardized myocardium. The PA beneficial effect on salvaged myocardium is also associated with less coronary microvasculature damage.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Imaging* online.

Conflict of interest: none declared.

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